

WHAT IS CLAIMED IS:

1. A polypeptide comprising hemoglobin alpha chain wherein the C-terminal hydrophobic domain has been substituted or deleted.
2. A polypeptide comprising hemoglobin alpha chain wherein the C-terminal haptoglobin-binding domain has been substituted or deleted.
3. A polypeptide comprising amino acids 1-97 of the human alpha hemoglobin chain.
4. A pharmaceutical composition comprising (a) a polypeptide as in claim 1 or 2 and (b) a pharmaceutically acceptable carrier.
5. A pharmaceutical composition comprising a polypeptide consisting of amino acids 1-97 of the human alpha hemoglobin chain and a pharmaceutically acceptable carrier.
6. A pharmaceutical composition comprising a polypeptide consisting of amino acids 1-94 of the human alpha hemoglobin chain and a pharmaceutically acceptable carrier.
7. A pharmaceutical composition as in claim 4-6 in unit dosage form.
8. A pharmaceutical composition as in claim 7 comprising 0.1 mgs. to 6 gms. of one or two compounds selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

9. A method of inhibiting stem cell proliferation comprising contacting hematopoietic cells with a stem cell proliferation inhibiting amount of a polypeptide as in claim 1 or 2.

10. A method as in claim 9 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain, a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain and a peptide having the sequence Phe-Leu-Gly-Phe-Pro-Thr.

11. A method of stimulating the growth of B cells which comprises contacting hematopoietic cells with a growth stimulating amount of a polypeptide as in claim 1 or 2.

12. A method of treating cancer in a mammal suffering therefrom comprising the steps of:

a) administering radiotherapy or chemotherapy, and

b) administering a stem cell proliferation inhibiting amount of a polypeptide

as in claim 1 or 2.

13. A method as in claim 12 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

14. A method as in claim 12 wherein steps a and b are repeated one or more times.

15. A method as in claim 12 wherein step a is conducted after step b.

16. A method as in claim 12 wherein step b is conducted within 24 hours before or after step a.

17. A method for treating cancer in a mammal comprising:

- a) removing hematopoietic cells from said mammal,
- b) treating said hematopoietic cells *ex vivo* with a polypeptide as in claim 1 or 2,
- c) treating said hematopoietic cells of step b with chemotherapy or radiation,
- d) performing myeloablative treatment on said mammal, and
- e) transplanting into said mammal the hematopoietic cells of step c.

18. A method as in claim 17 wherein said polypeptide in step (b) is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

19. A method of inhibiting stem cell division in a mammal exposed to an agent which damages or destroys stem cells comprising administering a stem cell proliferation inhibiting amount of a polypeptide as in claim 1 or 2.

20. A method as in claim 19 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain, a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain and a peptide having the sequence Phe-Leu-Gly-Phe-Pro-Thr.

21. A method as in claim 19 wherein said agent is an antiviral agent.

22. A method of maintaining mammalian hematopoietic stem cells *ex vivo* comprising contacting hematopoietic cells with a stem cell proliferation inhibiting amount of a polypeptide as in claim 1 or 2.

23. A method as in claim 22 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain, a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain chain, and a peptide having the sequence Phe-Leu-Gly-Phe-Pro-Thr.

24. A method as in claim 22 wherein said hematopoietic cells are selected from the group consisting of bone marrow cells, peripheral blood cells, mobilized peripheral blood cells, fetal liver and umbilical cord blood cells.

25. A method of treating a myeloproliferative or autoimmune disease or epithelial stem cell hyperproliferation in a mammal suffering therefrom comprising administering a hyperproliferative reducing amount of a polypeptide as in claim 1 or 2.

26. A method as in claim 25 wherein said myeloproliferative disease is a myelodysplastic syndrome.

27. A method for differentially protecting normal stem cells and not cancer cells in a mammal from chemotherapy or radiation comprising administering a stem cell protecting amount of a polypeptide as in claim 1 or 2.

28. A method as in claim 27 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain, a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain, and a peptide having the sequence Phe-Leu-Gly-Phe-Pro-Thr.

29. A method as in claim 27 wherein said polypeptide is administered after said normal stem cells are induced to proliferate by exposure to a cytotoxic drug or radiation.

30. A method of vaccinating a mammal comprising administering a polypeptide as in claim 1 or 2 as an adjuvant before, during or after administration of a vaccine.

31. A method of treating a mammal having immunodepression caused by stem cell hyperproliferation comprising administering to said mammal an hyperproliferation reversing amount of a polypeptide as in claim 1 or 2.

32. A method of conducting gene therapy in a mammal comprising:

- a) removing hematopoietic cells from said mammal,
- b) transfecting said hematopoietic cells with a predetermined gene,
- c) contacting said transfected hematopoietic cells *ex vivo* with a polypeptide as in claim 1 or 2
- d) transplanting into said mammal the hematopoietic cells of step c.

33. A method as in claim 32 wherein said polypeptide in step (c) is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

34. A method as in claim 32 further comprising after step (a) treating said hematopoietic cells with at least one stimulatory cytokine to induce stem cell proliferation.

35. A method as in claim 32 further comprising after step (d) treating the mammal *in vivo* with said polypeptide.

36. A method for conducting *ex vivo* stem cell expansion comprising contacting hematopoietic cells with a polypeptide as in claim 1 or 2 and at least one stimulatory cytokine.

37. A method as in claim 36 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

38. A method as in claim 36 wherein said hematopoietic cells are cells selected from the group consisting of bone marrow cells, peripheral blood cells, mobilized peripheral blood cells, fetal liver and umbilical cord blood cells.

39. A pharmaceutical composition comprising (a) a polypeptide as in claim 1 or 2 and (b) at least one inhibitory compound selected from the group consisting of MIP-1 α , TGF β , TNF α , INF α , INF β , INF γ , the pentapeptide pyroGlu-Glu-Asp-Cys-Lys, the tetrapeptide N-Acetyl-Ser-Asp-Lys-Pro, and the tripeptide glutathione (Gly-Cys- γ Glu).

40. A method as in claim 39 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

41. A pharmaceutical composition comprising (a) a polypeptide as in claim 1 or 2 and (b) at least one stimulatory compound selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-13, IL-14, IL-15, G-CSF, GM-CSF, M-CSF, erythropoietin, thrombopoietin, stem cell factor, and flk2/flt3 ligand.

42. A method as in claim 41 wherein said polypeptide is selected from the group consisting of a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

43. A method for expressing alpha hemoglobin or substitution or deletion analogs thereof comprising expressing said alpha hemoglobin or substitution or deletion analogs as a ubiquitin fusion.

44. A method as in claim 43 wherein said expressing step is done in *E. coli*.

45. A method as in claim 43 wherein said expressing step includes expressing a ubiquitin cleaving enzyme.

46. A peptide having the sequence selected from the group consisting of biotin-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val, (iodo)Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val, Phe-Pro-His-(iodo)Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val and (iodo)Phe-Pro-His-(iodo)Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val.

47. A method of stimulating stem cell proliferation comprising contacting hematopoietic cells with a stem cell proliferation stimulating amount of INPROL and/or an opiate compound.

48. A method as in claim 47 wherein said INPROL is selected from the group consisting of the alpha chain of hemoglobin, the beta chain of hemoglobin, the gamma chain of hemoglobin, the delta chain of hemoglobin, the epsilon chain of hemoglobin, the zeta chain of hemoglobin, a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain, and a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain.

49. A method as in claim 47 wherein said INPROL is selected from the group consisting of peptides having the sequence:

Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

Cys-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val-Cys

(where the two Cys residues form a disulfide bond),

Asp-Ala-Leu-Thr-Asn-Ala-Val-Ala-His-Val-Asp-Asp-Met-Pro-Asn-Ala-Leu-Ser-Ala,

Phe-Leu-Gly-Phe-Pro-Thr,

Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe,

Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg,

Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln,

Leu-Val-Val-Tyr-Pro-Trp-Thr,

Leu-Val-Val-Tyr-Pro-Trp,

Leu-Val-Val-Tyr-Pro,

Val-Val-Tyr-Pro-Trp-Thr-Gln,

Tyr-Pro-Trp-Thr-Gln-Arg-Phe,
Tyr-Pro-Trp-Thr-Gln-Arg,
Tyr-Pro-Trp-Thr-Gln, and
Tyr-Pro-Trp-Thr.

50. A method as in claim 47 wherein said opiate compound is selected from the group consisting of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

51. A method of stimulating stem cell proliferation comprising contacting hematopoietic cells with a compound capable of binding opiate receptors.

52. A method as in claim 51 wherein said compound has selectivity for the mu subclass of opiate receptor.

53. A method of stimulating or inhibiting stem cell proliferation comprising contacting hematopoietic cells with a compound capable of binding nociceptin receptors.

54. A method of stimulating or inhibiting stem cell proliferation comprising contacting hematopoietic cells with a compound capable of activating the G_i inhibitory subclass of GTP binding proteins.

55. A method of stimulating or inhibiting stem cell proliferation comprising contacting hematopoietic cells with a compound capable of binding to an opiate-like receptor not including the classical mu, kappa or delta opiate receptors or ORL1, wherein

said receptor (a) has stem cell stimulating and/or inhibiting properties and (b) has said stem cell stimulating and/or inhibiting ability antagonizable by naloxone.

56. A method as in claim 55 wherein said opiate-like receptor has the ability to bind the peptide Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val with a dissociation constant (K_d) less than or equal to 1 micromolar.

57. A method as in claim 55 wherein the dissociation constant is less than or equal to 10 nanomolar.

58. A method of identifying a receptor for INPROL comprising contacting a material which contains said receptor with INPROL in a receptor-binding assay.

59. A method as in method 58 wherein said INPROL is selected from the group
the alpha chain of hemoglobin, the beta chain of hemoglobin, the gamma chain of hemoglobin,
the delta chain of hemoglobin, the epsilon chain of hemoglobin, the zeta chain of hemoglobin,
a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain,
a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain,
Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,
biotin-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,
(iodo)Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,
Phe-Pro-His-(iodo)Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,
(iodo)Phe-Pro-His-(iodo)Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

Cys-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val-Cys, and
Asp-Ala-Leu-Thr-Asn-Ala-Val-Ala-His-Val-Asp-Asp-Met-Pro-Asn-Ala-Leu-Ser-Ala.

60. A method of identifying a receptor for INPROL comprising contacting a material which contains said receptor with INPROL in an adenylate cyclase assay.

61. A method as in method 60 wherein said INPROL is selected from the group
the alpha chain of hemoglobin, the beta chain of hemoglobin, the gamma chain of hemoglobin, the delta chain of hemoglobin, the epsilon chain of hemoglobin, the zeta chain of hemoglobin

a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain,

a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain,

Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

biotin-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

(iodo)Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

Phe-Pro-His-(iodo)Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

(iodo)Phe-Pro-His-(iodo)Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

Cys-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val-Cys, and

Asp-Ala-Leu-Thr-Asn-Ala-Val-Ala-His-Val-Asp-Asp-Met-Pro-Asn-Ala-Leu-Ser-Ala.

62. A method of treating cancer in a mammal suffering therefrom comprising the steps of:

a) administering radiotherapy and/or chemotherapy, and

b) administering a stem cell proliferation stimulatory amount of INPROL

and/or an opiate compound.

63. A method as in claim 62 wherein steps a and b are repeated one or more times.

64. A method as in claim 62 wherein step a is conducted before step b.

65. A method as in claim 62 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin..

66. A method of stimulating stem cell division in a mammal exposed to an agent which damages or destroys stem cells comprising administering a stem cell proliferation stimulating amount of INPROL and/or an opiate compound.

67. A method as in claim 66 wherein said agent is an antiviral agent or an anti-neoplastic agent.

68. A method as in claim 66 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

69. A method of maintaining mammalian hematopoietic stem cells *ex vivo* comprising contacting hematopoietic cells with a stem cell proliferation stimulating amount of INPROL and/or an opiate compound.

70. A method as in claim 69 wherein said hematopoietic cells are selected from the group consisting of bone marrow cells, peripheral blood cells, mobilized peripheral blood cells, fetal liver and umbilical cord blood cells.

71. A method as in claim 69 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

72. A method of treating a myeloproliferative disease, hematopoietic or epithelial stem cell hypoproliferation in a mammal suffering therefrom comprising administering a stimulatory amount of INPROL and/or an opiate compound.

73. A method as in claim 72 wherein said myeloproliferative disease is a myelodysplastic syndrome or aplastic anemia.

74. A method as in claim 72 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

75. A method for treating or preventing stem cell exhaustion comprising administering a stem cell proliferation inhibitory amount of INPROL and/or an opiate compound.

76. A method as in claim 75 wherein said stem cell exhaustion is due to an acquired immune deficiency syndrome.

77. A method as in claim 75 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

78. A method for differentially protecting normal stem cells in a mammal from chemotherapy or radiation comprising administering a stem cell protecting amount of an opiate compound.

79. A method as in claim 78 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

80. A method of conducting gene therapy in a mammal comprising:

- a) removing hematopoietic cells from said mammal,
- b) treating said hematopoietic cells *ex vivo* with a stem cell stimulatory amount of INPROL and/or an opiate compound,
- c) transfecting or infecting said hematopoietic cells with a predetermined gene,
- d) contacting said transfected hematopoietic cells *ex vivo* with a stem cell inhibitory amount of INPROL and/or an opiate compound,

e) transplanting into said mammal the hematopoietic cells of step d

f) optionally treating said mammal *in vivo* with a stem cell inhibitory or stimulatory quantity INPROL and/or an opiate compound.

81. A method as in claim 80 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

82. A method for conducting *ex vivo* stem cell expansion comprising contacting hematopoietic cells with a stem cell stimulatory amount of INPROL and/or an opiate compound.

83. A method as in claim 80 wherein said hematopoietic cells are cells selected from the group consisting of bone marrow cells, peripheral blood cells, mobilized peripheral blood cells, fetal liver and umbilical cord blood cells.

84. A method as in claim 80 wherein said opiate compound is selected from the group of morphine, etorphine, codeine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphine, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO, DALDA and nociceptin.

85. A pharmaceutical composition comprising (a) an opiate compound and (b) at least one inhibitory compound selected from the group consisting of MIP-1 α , TGF β , TNF α , INF α , INF β , INF γ , the pentapeptide pyroGlu-Glu-Asp-Cys-Lys, the tetrapeptide N-Acetyl-Ser-Asp-Lys-Pro, and the tripeptide glutathione (Gly-Cys- γ Glu).

86. A pharmaceutical composition comprising (a) an opiate compound and (b) at least one stimulatory compound selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-13, IL-14, IL-15, G-CSF, GM-CSF, M-CSF, erythropoietin, thrombopoietin, stem cell factor, and flk2/flt3 ligand.

87. A method of treating pain in a mammal comprising administering to said mammal an analgesia-inducing amount of INPROL.

88. A method as in method 87 wherein said INPROL is selected from the group the alpha chain of hemoglobin, the beta chain of hemoglobin, the gamma chain of hemoglobin, the delta chain of hemoglobin, the epsilon chain of hemoglobin, the zeta chain of hemoglobin,

a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain,

a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain,

Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

Cys-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val-Cys, and

Asp-Ala-Leu-Thr-Asn-Ala-Val-Ala-His-Val-Asp-Asp-Met-Pro-Asn-Ala-Leu-Ser-Ala.

87. A method of treating immune deficiency in a mammal comprising administering to said mammal an immunostimulatory amount of INPROL.

88. A method as in method 87 wherein said INPROL is selected from the group the alpha chain of hemoglobin, the beta chain of hemoglobin, the gamma chain of hemoglobin, the delta chain of hemoglobin, the epsilon chain of hemoglobin, the zeta chain of hemoglobin,

a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain,

a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain,

Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val,

Cys-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val-Cys, and

Asp-Ala-Leu-Thr-Asn-Ala-Val-Ala-His-Val-Asp-Asp-Met-Pro-Asn-Ala-Leu-Ser-Ala.